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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ART UNIT	PAPER NUMBER
1632	

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/446,913	ONO ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed January 3, 2003 (Paper No. 15) has been entered. Claims 5-24 have been newly added. Claims 1-4 have been cancelled.

Accordingly, Claims 5-24 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 14 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly added claims include new matter.

Claim 14 recites elements without support in the original disclosure, thereby adding new matter to the claims. The claim recites "wherein said NF-κB decoy is a modified nuceleotide or a pseudonucleotide." There is nothing in the specification that suggests NF-κB would bind to a single nucleotide, whether a modified nucleotide or pseudonucleotide. Rather, the specification only

contemplates **an oligonucleotide that contains** a modified nucleotide or a pseudonucleotide (sentence bridging pages 4-5).

Claim 16 recites elements without support in the original disclosure, thereby adding new matter to the claims. The claim recites "wherein said NF-κB decoy comprises multiple units of a nucleotide or nucleotide analog." There is nothing in the specification that suggests NF-κB would bind to multiple units of a nucleotide or nucleotide analog. The term "multiple units of a nucleotide" is understood to mean repeating units of a nucleotide, for example an polyA oligonucleotide. No support for a decoy comprising multiple units of a nucleotide or nucleotide analog is found in the specification. Applicants have pointed to the specification at pages 4-5 and the first paragraph of page 6 as support for this claim, but no support is found. The specification only contemplates an NF-κB decoy that is "a double-stranded oligonucleotide containing one or several units of said nucleotide sequence" at page 5, paragraph 1.

Thus, the claimed invention is not adequately described in the specification as-filed and the amendment introduces new matter into the claims.

Written Description

Claims 5-16 and 18-24 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record as applied to Claims 1-4 as set forth on pages 2-3 of the Office Action of Paper No. 11 (mailed 7/3/02), as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants are referred to the guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

The claims are directed to a method for treating or preventing a brain disorder by administering an effective amount of an NF-κB decoy. However, no particular structural limitations are recited for the

decoy in Claims 5-8 and 18-24 and only very large genuses of nucleic acid molecules are recited in Claims 9-16. Thus, the claims are broadly directed to any compound that functions in the manner intended, i.e. in protecting the brain through some type of interaction with NF-κB. All claims recite an intended use, i.e. that the agent can be used for brain protection (although no treatment effect is required). The claims cover a very large genus of compounds, but only a single species is described in the specification. The NF-κB decoy is an essential element of the claimed invention. As such, it must be adequately described in the specification. The Guidelines for Written Description specifically state that "[t]he claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art" (Federal Register, Vol. 66, No. 4, page 1105, column 1).

However, the specification does not provide a written description of any substance that can be used for brain protection other than SEQ ID NO: 1. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only SEQ ID NO: 1 is disclosed as an agent that acts as an NF-κB decoy and provides protection against particular types of brain damage when delivered using a cationic liposomal delivery system. SEQ ID NO: 1 is described as a rabbit NF-κB recognition sequence. The specification does not describe other targets for other species. Moreover, no other brain-protective agents of the type claimed are described. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, the specification does not describe any other brain-protective agents by other relevant identifying characteristics.

A nucleic acid molecule is a complex chemical compound, and it is well-established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials. See *Oka* 7 USPQ2d at 1171. Conception does not occur unless one has a mental

picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinquish it. **It is not sufficient to define it solely by its principal biological property**, because an alleged conception having no more specificity than that **is simply a wish to know the identity of any material with that biological property**. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the genus of brain-protective agents claimed, at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus of NF-κB decoys that can be used as brain-protective agents.

At page 4 of the response, Applicants argue that this rejection does not apply to the newly added claims because of the conventional nature of the term "NF-κB decoy." As evidence of the conventional nature of this term Applicants point to Claim 203 of U.S. Patent No. 6,410,516. However, this reference was published in 2002 cannot be used to suggest that what was disclosed therein was known in the art and conventional at the time of filing of this application, which claims priority to 1997. Applicants further state that the reference describes decoys and methods for identifying decoys. Again, these would not have been known in the art at the time of filing the instant application because this reference was not published until 2002. Applicants further assert that the instant specification exemplifies an NF-κB decoy at page 12, line 4. The Examiner has already acknowledged disclosure of SEQ ID NO: 1 (see pages 2-3 of the Office Action of Paper No. 11 and reasons reiterated herein above), but as the only species described within a very large genus. Disclosure of a single species within a very large genus is not sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the genus of NF-κB decoys covered in the claims, at the time the application was filed.

Applicants further argue that NF-κB decoys could be identified as described in the specification without undue experimentation. No support is offered for this assertion. Moreover, providing a method

for identifying agents having a specific function does not constitute a written description of the agent itself. It is not sufficient to define an agent solely by its principal biological property, because an alleged conception having no more specificity than that **is simply a wish to know the identity of any material with that biological property**. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

Enablement

Claims 5-24 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 3-6 of the Office Action of Paper No. 11 (mailed 7/3/02), because the specification, while being enabling for (i) a method of diminishing cerebral vasospasm associated with subarachnoid hemorrhage by administering an agent comprising SEQ ID NO: 1 and a liposomal delivery system and (ii) a liposome comprising a double-stranded nucleic acid oligonucleotide having the sequence set forth in SEQ ID NO: 1, does not reasonably provide enablement for a method for treating or preventing any brain disorder by administering any agent that functions as an NF-κB decoy nor does it provide enablement for a composition that does not include the double-stranded oligonucleotide of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At page 4 of the response, Applicants dismiss the enablement rejection because they believe that failures in gene therapy have been in fields unrelated to the administration of NF-κB decoys. This argument is not found persuasive because the art of gene therapy, which involves delivering a nucleic acid to produce a therapeutic effect, as required for the instantly claimed methods, is certainly the relevant area of art for the enablement inquiry here. The instantly claimed methods are clearly directed to the *in vivo* delivery of a nucleic acid molecule for the purpose of producing a therapeutic effect, i.e. treating or preventing a brain disorder. Applicants further argue that the specification has actually shown that

administration of an NF-κB decoy treats brain disease. The Examiner has already indicated an enabled scope commensurate with the teachings of the specification.

At page 5, paragraph 2 of the response, Applicants argue that administration of an NF-κB decoy does not require expression of a gene. However, the claimed method still requires delivery of the agent, specifically the nucleic acid of SEQ ID NO: 1, to the appropriate tissues in order to produce a therapeutic effect. For reasons of record, targeting appropriate tissues for nucleic acid delivery, particularly delivery of an amount sufficient to provide a therapeutic effect, is highly unpredictable. Furthermore, although not contemplated in the specification, the claims broadly encompass delivery of a nucleic acid that encodes an NF-κB decoy, such as a protein that binds NF-κB. Contrary to Applicants assertion, in such a case, expression of a gene would be required.

At page 5, paragraph 3 of the response, Applicants argue that on pages 11-13, the specification provides a working example. However, this example is the subarachnoid hemorrhage model which the Examiner has already indicated as being enabled.

At page 5, paragraph 4, Applicants assert that given the single working example of the specification, one of skill in the art would be able to select appropriate brain diseases and appropriate forms and sites of administration for treatment of a subject without undue experimentation. No support is offered for this assertion. Applicants assert that the data of the specification show that liposomal products are suitable at least for treating vascular narrowing associated with subarachnoid hemorrhage. However, the composition claims cover liposomes comprising any agent that functions as an NF-κB decoy, whereas only SEQ ID NO: 1 has been shown to be useful for producing a therapeutic effect. For reasons of record, given the limited guidance in the specification, particularly with regard to the agent that is to be delivered, the quantity of experimentation necessary to determine appropriate parameters for carrying out the claimed method using any agent with the function recited in the claims, and further given the lack of applicable working examples demonstrating an *in vivo* effect for brain disorders other than cerebral

vasospasms associated with subarachnoid hemorrhage, and the unpredictability for using the method to treat or prevent the wide variety of brain disorders set forth in the specification, undue experimentation would have been required for one skilled in the art to practice the claimed invention and make and use the claimed compositions over the full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-24 are indefinite in their recitation of an "NF-κB decoy" because it is unclear what would constitute an "NF-κB decoy." The specification indicates on page 3 that an NF-κB decoy is a compound that specifically competes with the nucleic acids to which NF-κB binds. However, this definition is non-limiting and does not refer to any particular structure that would carry out the function set forth in the definition. Thus, the metes and bounds of the decoy are not clearly set forth.

Claims 5-17 and 24 are indefinite in their recitation "[a] method for treating or preventing a brain disorder" in the preamble because the body of the claim only sets forth a single step where an agent is administered to a subject, but no treatment effect is achieved or required. Thus, the body of the claim is in conflict with the preamble.

Claims 10-12 are indefinite in their recitation of "or nucleic acid analog" because it is unclear what the nucleic acid analog is an analog of. For example, Claim 10 recites "a double-stranded nucleic acid or nucleic acid analog" but there is no requirement that the analog is in any way related to the double-stranded nucleic acid first recited in the claim and there is no requirement that the nucleic acid analog be of any particular form, i.e. double-stranded, single-stranded, or cyclic.

Claim 16 is indefinite in its recitation of "comprises multiple units of a nucleotide or nucleotide analog" because it is unclear what would constitute "multiple units of a nucleotide." It would appear that the term could cover any oligonucleotide that has two G nucleotides or two C nucleotides. In this case, the claim would cover any oligonucleotide over 5 nucleotides in length, since there are only 4 different nucleotides. Thus, an oligonucleotide of the form CATGC would comprise multiple units of a nucleotide because is has two C nucleotides. Alternatively, the term could be taken to mean that the decoy comprises repeating units of a nucleotide such as a polyA oligonucleotide. Thus, the metes and bounds of the claim is not clearly set forth.

Claim 24 is indefinite in its recitation of "administering **and** effective amount" because the term "and" appears to be a typographical error.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-16 and 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,410,516 (Baltimore et al., 2002).

Baltimore et al. (2002) disclose a method of inhibiting expression, in a mammalian cell, of a gene whose transcriptional activity is activated by binding of NF-κB to said gene, comprising introducing a nucleic acid decoy molecule into the cell in an amount sufficient to inhibit expression of the gene, which decoy includes a NF-κB binding site that binds to NF-κB. See Claim 203.

Although the reference does not teach treatment of a brain disorder, no treatment effect is achieved or required by the instant claims.

With regard to the method claims, this rejection could be overcome by reciting a specific treatment effect in the claims.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER